CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CHLORONEB

SB 950-035, Tolerance # 257
3/13/87
Revised 6/1/88; 7/17/89

I. DATA GAP STATUS

Chronic rat: Data gap, inadequate study, no adverse effect indicated

Chronic dog: Data gap, inadequate study, possible adverse effect indicated

Onco rat: Data gap, no study on file

Onco mouse: Data gap, no study on file

Repro rat: Data gap, inadequate study, no adverse effect indicated

Terato rat: Data gap, inadequate study, no adverse effect indicated

Terato rabbit: Data gap, inadequate study, possible adverse effect indicated

Gene mutation: No data gap, no adverse effect

Chromosome: Data gap, inadequate study, no adverse effect indicated

DNA damage: Data gap, inadequate study, no adverse effect indicated

Neurotox: Not required at this time.

----------**Note, Toxicology one-liners are attached**

** indicates acceptable study
Bold face indicates possible adverse effect
File name = T890717

Revised by G.F. Chernoff, July 17, 1989

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED

RAT

(No study)

CHRONIC

RAT

002 33185. Chronic Rat - 831 (Rec. #947479-2 in original review). Date and location of study (1 page summary) not given - possibly Haskell Lab study #201-124, 7/8/68, judging from EPA 1-liners. Chloroneb purity not stated, fed at 100, 500 or 2500 ppm in diets of 36/sex/group. No apparent adverse effects indicated. Apparent NOEL = 500 ppm (markedly reduced growth in 2500 ppm females). NOT ACCEPTABLE, NOT UPGRADEABLE: Too few animals/group for combined or oncogenicity study and insufficient information presented for evaluation. (J. Remsen (Gee), 3/13/85).

EPA one-liner: Oncogenic NOEL > 2500 ppm (HDT); Systemic NOEL = 500 ppm; Systemic LEL = 2500 ppm (HDT; growth suppression and food consumption reduced). Levels tested at 0, 100, 500 or 2500 ppm.

DOG

002 947479 . Chronic Dog - 1 page summary of study. Date and location of study not given - possibly Hazleton Lab; #201-124, 7/8/68, judging from EPA 1-liners. Chloroneb purity not stated, administered in diets at 0, 100, 500, 2500, and 10000 ppm to 4/sex/group. Apparent NOEL = 500 ppm. (Summary reads: "Compound-related histopathological alterations were found in livers, thyroids, and stomachs of some dogs in Group 4 (2500 ppm) only". NOT ACCEPTABLE, NOT COMPLETE due to insufficient information for assessment. (J. Remsen (Gee), 3/13/85).

EPA one-liner: Systemic NOEL = 500 ppm; Systemic NOEL = 2500 ppm (increased SGPT, SAP). Levels tested = 0, 100, 500, 2500 and 10,000 ppm.

ONCOGENICITY

RAT

(No studies)

MOUSE

(No studies)

REPRODUCTION

RAT

014 36470, "Chloroneb: 3-generation Rat Reproduction Study", (Hazleton Laboratory, Vienna, VA, 5/25/67 - Supplement: individual animal data portion of study). Chloroneb (Fungicide 1823), 75% WP and 65% WP used: reported dosages based on % a.i. in diet. 0, 100, and 500 ppm in diet. Apparent NOEL for parental and reproductive effects = 500 ppm (no toxicity). NOT ACCEPTABLE, NOT UPGRADEABLE: Technical material not used, dosages not justified and apparently far below MTD (based on comparison with reported toxicity from other rat studies); no study protocol, no diet analysis of test article levels, stability, and homogeneity; no histopathology data presented. (J. Remsen (Gee), 11/6/85).

EPA one-liner: Doses tested: 0, 100 500 ppm (feed).
Data inadequate for establishment of reproductive NOEL: only two dose levels, inappropriate protocol, inadequate description of methods, no individual necropsy data, no record of parental weight change.

002 947480 and 017 42786 are summaries of 014 36470.

TERATOGENICITY

RAT

015 36471, "Embryo-fetal Toxicity and Teratogenicity Study of Chloroneb in the Rat", (Argus Research Labs, 6/27/83). Chloroneb, 90% purity suspension in aqueous Methocel administered at 0, 300, 1000, and 3500 mg/kg/day by gavage in Crl: COBS CD(SD)BR rats. No developmental toxicity observed. Maternal toxicity NOEL $\leq$ 300 mg/kg/day (salivation significantly increased at 1000 and 3500 mg/kg/day, stained abdominal fur at 3500 mg/kg/day). NOT ACCEPTABLE,

UPGRADEABLE: Needs analysis of dosing solution on first and last day, which was performed by the sponsor, but data not included in the report as presented. (J. Remsen (Gee), 11/6/85).

EPA one-liner: Doses tested: 0, 300, 1000, 3500 mg/kg/day (gavage) in CrL:COBS.CD. (SD) BR strain. Teratogenic NOEL>3500 mg/kg/day (HDT). Maternal NOEL, maternal LEL, fetotoxic LEL and fetotoxic NOEL will be determined after submission of additional data as requested from registrant.

020 69899 "Embryo-Fetal Toxicity and Teratogenicity Study of Chloroneb in the Rat", (Argus Research Labs, 6/27/83). The concentration of Chloroneb, 90% pure, was determined in frozen samples of dosing solutions (0, 30, 100, 300, and 350 mg/ml), collected during a pilot and main rat teratology study. Using RPLC, each sample was found to contain at least the theoretical concentration of chloroneb. NOT ACCEPTABLE, UPGRADEABLE: An analysis of the a.i. composition in the dosing solution is needed. Supplemental to 36471. (Chernoff 7/10/89)

RABBIT

020 68719 "Rabbit Teratology Study with Chloroneb (Technical Grade)", (Hazleton, 6/1/88). Technical chloroneb, 91.8% pure in 0.5% methyl cellulose was administered by gavage to groups of 16 inseminated New Zealand White Rabbits at 0, 10, 100 or 1000 mg/kg/day on days 7-19 of gestation. **Possible adverse effects:** Developmental toxicity (increased skeletal anomalies, increased ventral midline anomalies, and decreased fetal weight.). Developmental NOEL = 100 mg/kg/day, maternal NOEL = 100 mg/kg/dy (marginal decreased body weight and late onset post treatment anorexia). NOT ACCEPTABLE, UPGRADEABLE: Needs analysis of dosing solution on first and last day, which was performed by the sponsor, but data not included in the report as presented. (Chernoff, 7/11/89).

GENE MUTATION

016 36472, "Mutagenicity Evaluation in Salmonella typhimurium", (Haskell Labs, 2/20/81 - Report No. 147-81). Chloroneb purity not stated, tested 0 to 500 ug/plate on strains TA98, TA100, TA1535, and TA1537 with and without activation. **TEST POSITIVE for TA100 in presence of S9 (however degree of increase in revertant frequency was small (1.6-fold at most). Finding determined by CDFA reviewer to be of doubtful biological significance. Study ACCEPTABLE. (J. Remsen (Gee), 11/6/85).

EPA one-liner: Negative for TA 1535, 1537 and 98 strains (with activation). Positive for TA 100 (without activation) (10 and 25 ug/plate). Dose = 0, 1, 5, 25, 50, 100 or 500 ug/plate. ACCEPTABLE.

**016 36474, "Chinese Hamster Ovary Cell Assay for Mutagenicity", (Haskell Laboratory, (HGPRT mutation study) - report no. 834-1, 12/9/81. Chloroneb purity not stated, tested at 0-722 ug/ml. Two (2) trials with and eight (8) without activation. TEST NEGATIVE: no consistent increase in mutation frequency in replicate trials. ACCEPTABLE. (Remsen (Gee), 11/6/85).

EPA one-liner: Negative, ACCEPTABLE.

NOTE: A weak positive response was observed in the "Ames" test (016:36472) for strain TA100, so that the study indicated a **"possible adverse health effect"**, albeit of "doubtful" biological significance. A subsequent ACCEPTABLE in vitro mammalian cell mutagenicity study (016:36474) was negative. These two studies together do not indicate a mutagenic risk to humans.

CHROMOSOME

016 36473, "Mutagenicity Evaluation of 13,921 in an In Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (Litton Bionetics, report no. 20990, 5/81). Chloroneb purity not stated, tested at 0-500 ug/ml with and without rat liver activation, exposed 2 or 8.5-10 hr, respectively; TEM and cyclophosphamide controls. Test negative: No increase in aberrations reported in first cell cycle. NOT ACCEPTABLE, UPGRADEABLE: needs mitotic index to show if cycle delay, indication of whether system tested for mycoplasma, data from first trial which was not included in the present report. (J. Remsen (Gee), 11/6/85).

EPA one-liner: Negative, ACCEPTABLE.

DNA DAMAGE

016 36475, "The Hepatocyte Primary Culture/DNA Repair Assay on Compound 13921 Using Rat Hepatocytes in Culture", (Naylor Dana Institute, 11/15/81). Chloroneb purity not stated, treatment levels: 0 (DMSO), 0.1, 1, 10, 100, and 1000 ug/ml. Two independent tests with three replicates/test. Test negative (no increase in net grain counts on nuclei). NOT ACCEPTABLE, UPGRADEABLE: needs additional data (a) numbers of nuclei counted per sample (b) number of nuclei in S phase (c) clarify whether or not serum was present during treatment. (J. Remsen (Gee), 11/6/85).

EPA one-liner : Negative. ACCEPTABLE.

NEUROTOX

Not required at this time.